Article

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Abstract

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Review article

Vitamin D in Adolescents: A Systematic Review and Narrative Synthesis of Available Recommendations

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A B S T R A C T

Purpose: Practical guidelines help clinicians make their preventive and therapeutic choices and improve care management. Our purpose was to collect and synthesize available recommendations concerning vitamin D in adolescents (aged 10–19 years).
Methods: We searched PubMed, EMBASE, and Cochrane databases from inception to February 5, 2019, for guidance published by different professional associations and governments. We also searched the reference lists of identified recommendations and explored the gray literature using Web search engines. We organized documents by theme: dietary requirements, thresholds, prophylactic supplementation, and treatment of deficiency.
Results: A total of 32 documents were identified. Most of them targeted the general population and not specifically the age group of adolescents. There is a general agreement that adolescents should not have serum 25-hydroxyvitamin D concentrations below 25–30 nmol/L to avoid poor bone health. However, there is lack of consensus on the optimal concentration to aim for, levels varying between 25 nmol/L and 150 nmol/L. Adequate nutritional requirements of vitamin D are also subject to debate with values ranging between 200 IU/d and 1,000 IU/d. The upper tolerable intake is estimated at 4,000 IU/d by all study groups. Certain associations recommend routine vitamin D supplementation in adolescents. The recommended daily preventive doses vary between 400 IU and 4,000 IU, depending on season, skin pigmentation, sun exposure, consumption of vitamin D–fortified foods, body mass index, and coexistence of certain medical conditions. In case of deficiency, different therapeutic regimens of oral vitamin D are proposed depending on the presence of illness and/or the baseline serum 25-hydroxyvitamin D concentrations. Duration of the treatment varies between 4 weeks and 3 months. A maintenance dose is generally recommended after treatment.
Conclusions: At present, there is no consensus among the different societies about vitamin D needs during adolescence. Stronger, evidence-based guidance is needed to inform clinical practice.

IMPLICATIONS AND CONTRIBUTION

These findings illustrate a global lack of consensus about the identification, prevention, and management of vitamin D deficiency in adolescence. In the absence of sufficient high-quality studies, most available guidelines are unable to fulfill criteria for optimal guideline development.

Importance of vitamin D during childhood and adolescence

Vitamin D plays a key role in bone accretion. Together with calcium intake and physical activity, it promotes maximal bone health from childhood to adolescence and determines peak bone mass development [1]. Persistent severe vitamin D deficiency

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(VDD) is known to result in altered mineralization of the skeleton. This can lead to classical index diseases, that is, rickets in children and osteomalacia in adults. However, there is now evidence suggesting that even subclinical VDD may affect bone acquisition, potentially beginning in utero and extending into adolescence [2,3]. Ensuring adequate vitamin D status during adolescence is crucial to maximize peak bone mass and, thus, reduce the impact of age-related bone loss.

In addition, the extraskeletal actions of vitamin D have raised great interest [4]. Following the discovery of vitamin D receptors in many typical human tissues, low levels of vitamin D have been associated with many infectious [5,6], autoimmune [7,8], and cardiovascular diseases [9], even with cancerous conditions [10]. Observational studies have shown inverse associations between vitamin D status and all-cause mortality [11,12]. Findings from randomized interventions remain inconsistent and, at present, universal vitamin D supplementation does not seem justified for the prevention and treatment of nonskeletal disorders in healthy individuals [13].

Prevalence of VDD in adolescence

VDD has been classified as a widespread pandemic and is considered the most common nutritional deficiency worldwide [14]. Findings about vitamin D status in adolescence are inconsistent, and available data from different studies are not easily comparable because of the use of different age groups, ethnicities, screening seasons, latitudes, analytical screening techniques, and, most of all, the use of different cutoff levels defining deficiency. Thus, the prevalence of VDD in adolescence varies worldwide from 4% to 91% [15–22] and is highlighted as an important public health concern even in sunny areas [17,23]. Nutritional rickets (NR) in adolescence not only remains a concern in low- and middle-income countries [24] but is also observed in Western societies, particularly in adolescents of African or Asian descent [25–27].

Evaluating vitamin D status in adolescent patients

In clinical practice, vitamin D status is usually determined in adolescent patients who are at high risk for VDD (e.g., who are obese and have particular medical conditions or a dark skin complexion). The number of consultations concerning these specific adolescent subgroups has remarkably risen in Western countries because of the increasing prevalence of obesity, the appropriate health care of patients with chronic conditions, and the international migration. Meanwhile, conflicting data about the potential extra-skeletal health benefits of vitamin D have resulted in elevated research interest. As a consequence, the increase in vitamin D testing and VDD treatment has significantly affected all health care systems globally [28,29].

Guidelines for the prevention and treatment of VDD in adolescents: a wide and diverse array of recommendations

Certain countries have established reports concerning the nutritional requirements for vitamin D as well as the optimal vitamin D status in the general healthy population. National and international scientific societies have developed recommendations for clinical practice regarding both the prevention and the treatment of VDD. Adolescents, in particular, represent a relatively neglected age group both in terms of preventive and therapeutic care and in terms of clinical research. Specific clinical recommendations for this vulnerable age group are limited and are often based on data arising from studies being conducted among younger children or adults. The extent to which these recommendations can be applied to adolescent patients remains unclear.

Aims of this review: to identify and synthesize all guidance about vitamin D in adolescents

Taking into account all these considerations, our purpose was to identify and synthesize all available recommendations concerning vitamin D in adolescents. We sought to examine all the guidance developed by scientific societies and governments from different regions of the world and to explore their level of consensus or the potential discrepancies in order to inform clinicians who deal with adolescents of all available preventive and therapeutic choices.

Methods

Design and search strategy

We conducted a systematic review and narrative synthesis of the literature. We searched the following scientific databases: PUBMED, EMBASE, and COCHRANE from inception to February 5, 2019 for published documents concerning vitamin D recommendations in the adolescent population. We used the following search terms for the title: (vitamin D OR NR) AND (guideline OR recommendation OR consensus OR statement). We additionally searched for relevant links and citations through hand screening of all reference lists. We also searched for gray literature, using Web search engines, that is, Google and Yahoo.

Selection criteria

All reports that examined vitamin D guidance in adolescents were eligible for inclusion. We defined adolescents as those aged between 10 and 19 years according to the World Health Organization definition. Because of the limited number of publications regarding this particular age group, we also considered reports concerning recommendations for the general population. We screened them by hand to identify specific guidance for the adolescent subgroup. We also included recommendations targeting children as far as they were covering the full range of childhood, namely from birth to 18 years.

We considered all reports published in the English and the French language. We excluded older versions of the reports if previously issued by the same organization.

The selection of documents for eligibility was evaluated independently by the two reviewers, first using title and abstract, and subsequently using the full text.

Outcomes

We extracted the data and made a narrative synthesis of the recommendations by organizing them thematically into four categories: (1) vitamin D status; (2) nutritional intake; (3) prophylactic supplementation; and (4) treatment of VDD.

Results

Identification of guidelines for the review

Figure 1 presents the flow diagram of the selection process. Thirty-two documents [30–61] reporting guidance on vitamin D in adolescents met our inclusion criteria and were considered for analysis (Table 1).

The majority of papers (24 of 32) were published by scientific societies [30–35,39,40,43–48,50,51,53–55,57–61], the others being reports established by departments of health [36–38,41,42,49,52,56]. One-third [30–42] provided an explicit description of the type and strength of the evidence used to develop the relevant recommendations. The other documents were position statements [45,47,48,59], endorsements of previously published guidance [50,61], overviews of available scientific data [46,54,55,60], practical advice [49,51,52,56], or experts' opinions [43,44,53,57,58].

We identified almost one reference for every continent. Only one document (Society of Adolescent Health and Medicine [SAHM]) [45] concerned guidance about vitamin D specifically in adolescence, whereas all other 31 documents were global recommendations, such as those targeting the entire pediatric population (10 documents) [34,40,44,47,48,51,54,58–60], or those concerning children and adult populations as a whole (21 documents) [30–33,35–39,41–43,46,49,50,52,53,55–57,61]. Half of these global recommendations provided separate considerations for the adolescent age group.

We identified six study groups that issued guidelines applicable to patients with particular chronic diseases, namely NR (Global Consensus [GC], Italian Pediatric Society [IPS], Indian Academy of Pediatrics [IAP], and American Academy of Pediatrics [AAP]) [30,40,58,60], cystic fibrosis (CF; Cystic Fibrosis Foundation [CFF]) [32], and chronic kidney disease (CKD; European Society of Pediatric Nephrology [ESPN]) [34]. The other documents included either recommendations for healthy populations or a mixture of guidance for both healthy individuals and groups at risk for VDD.

Definition of vitamin D status

We identified 23 documents [30–34,36–40,42,45,48,50,51,53–59,61] concerning 25(OH)D thresholds (Table 2). The level of the main circulating metabolite of vitamin

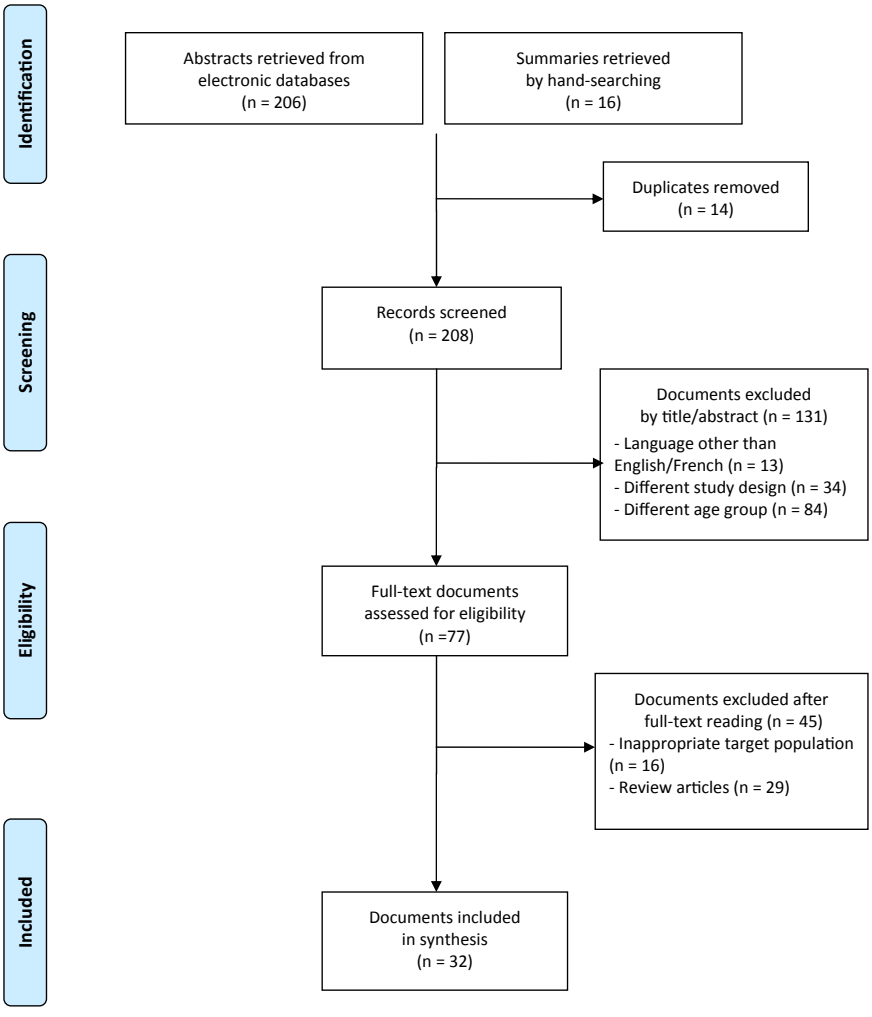

Figure 1. Summary of the selection process used in the review of recommendations.

Table 1
Overview of available recommendations regarding vitamin D in adolescents

Country	Organization/reference	Year of publication	Population	Type of recommendation	Guidelines development process
Reports with description of the type and strength of evidence used to develop the recommendations					
Global	Consensus of 11 societies on NR [30]	2016	All ages	■ 25(OH)D thresholds ■ RDAs for vitamin D ■ Supplementation policy ■ Treatment doses for NR	Global consensus on prevention and management of NR developed by 11 scientific societies mainly pediatric endocrine. Recommendations based on the GRADE system. In most circumstances, the recommendations were considered as strong.
Global	ES [31]	2011	All ages	■ 25(OH)D thresholds ■ RDAs and UIs ■ Treatment doses for VDD *Remarks: Screen 25(OH)D in patients at risk.*	Guidelines based on two systematic reviews of evidence. The Task Force developed recommendations based on the GRADE system. Most recommendations were considered as weak. Emphasis on patients at risk for VDD.
Global	CF Foundation [32]	2012	All ages	■ 25(OH)D optimal level ■ Treatment doses for VDD *Remarks: Screen 25(OH)D yearly in patients with CF.* *Cholecalciferol D3 should be preferred over ergocalciferol D2*	Multidisciplinary committee provided recommendations for CF patients based on a systematic review of evidence. The U.S. Preventive Services Task Force system was used to grade the evidence. Most recommendations were consensus opinions.
Europe	European Panel on Dietetic Products, Nutrition and Allergies [33]	2016	All ages	■ 25(OH)D target level ■ AIs	European panel set DRVs based on a meta-regression analysis of dose–response models.
Europe	European Society of Pediatric Nephrology (ESPN) [34]	2017	Children	■ 25(OH)D thresholds ■ Treatment doses for VDD *Remarks: Screen 25(OH)D in children with CKD once-twice a year.*	The working group developed clinical practice recommendations about native vitamin D use in children with CKD stages 2–5 and on dialysis based on the GRADE system. Most recommendations were considered as weak.
UK (England, Scotland, Wales, Ireland)	National Institute for Health and Care Excellence (NICE) [35]	2016	All ages	■ Supplementation for groups at risk *Remarks: Test vitamin D status only if someone has symptoms of deficiency or is at particularly high risk.*	Public health guideline aimed to increase supplement use among specific population groups to prevent VDD. Guideline was based on systematic reviews and on economic modeling. NICE methodology checklist was used.
	Scientific Advisory Committee on Nutrition (SACN) [36]	2016	All ages	■ 25(OH)D protective level ■ RNIs for children aged ≥4 y and adults SIs for infants and children aged <4 y	The Committee considered the data included in the 2011 IOM report together with evidence published since then. Evaluation of the evidence was based on the SACN's Framework for the Evaluation of Evidence. Recommendations applicable to the general healthy population including any at-risk groups.
Nordic Countries	Nordic Council of Ministers [37]	2012	All ages	■ 25(OH)D thresholds ■ RDAs and UIs	Recommendations based on evidence-based approach. Grading of the evidence according to the World Cancer Research Fund criteria. Recommendations targeted healthy individuals.
The Netherlands	Health Council of the Netherlands [38]	2012	All ages	■ 25(OH)D target value ■ AIs and UIs ■ Supplementation policy	Committee of experts set DRVs based on the SIGN grading system of evidence.

Table 1
Continued

Country	Organization/reference	Year of publication	Population	Type of recommendation	Guidelines development process
Poland	Polish Society of Pediatric Endocrinology and Diabetes and Expert Panel [39]	2018	All ages	■ 25(OH)D thresholds ■ UIs ■ Supplementation doses *Remarks: Screen 25(OH)D in risk groups. If testing is not possible, supplementation dose should be carried out according to the guidelines for the general population at the maximal doses for a given age group.*	Recommendations based on systematic literature search using the GRADE system. Combination of both strong and weak recommendations. Guidance for both the general population and groups at risk.
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Infants Children Adolescents	■ 25(OH)D thresholds ■ UIs ■ Supplementation doses for children at risk ■ Treatment doses of nutritional rickets and asymptomatic VDD *Remarks: Screen 25(OH)D in presence of multiple risk factors.*	Consensus opinion of experts based on the NIH Consensus Conference method and the Italian National Programme Guidelines. Recommendations considering both skeletal and extraskeletal effects of vitamin D.
Australia and New Zealand	Ministry of Health [41]	2006	All ages	■ AIs and UIs	Review based on the National Health and Medical Research Council system of evidence assessment. Reference to the 2004 U.S./Canadian DRIs and recommendations from other countries (UK 2003, Germany 2002) or key organizations (WHO 2001). Recommendations targeted healthy people.
U.S. and Canada	Institute of Medicine (IOM) [42]	2011	All ages	■ 25(OH)D thresholds ■ AIs for infants, RDAs for all other ages UIs for all ages	IOM Committee established DRIs for the generally healthy U.S. and Canadian populations. IOM focused on two evidence-based systematic reviews, which were conducted by the Agency for Healthcare Research and Quality and conducted its own literature review. Evidence maps were developed to assist the committee in organizing its review of the evidence.
Reports that provide no clear indication of how the evidence was assessed					
Global	WHO jointly with the Food and Agriculture Organization of the United Nations [43]	2004	All ages	■ RNIs	Experts' consultation decided to use the same figures that were recommended as AIs by the U.S. agencies in 1997.
Global	International Expert Group [44]	2015	Infants Children Adolescents	■ RDAs ■ Supplementation approaches	Experts' statement to summarize the state of the art on vitamin D and to suggest a practical approach to vitamin D supplementation during childhood and adolescence.
Global	Society for Adolescent Health and Medicine (SAHM) [45]	2013	Adolescents	■ 25(OH)D thresholds ■ Supplementation doses ■ Treatment dose for adolescents with VDD *Remarks: Screen 25(OH)D in adolescents at risk. Treat with a D3 preparation.*	Position statement.
Europe	European Panel on Dietetic Products, Nutrition and Allergies [46]	2012	All ages	■ UIs	European panel established UIs based on literature review. UIs for adolescents were set identical to UIs for adults.

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Table 1
Continued

Country	Organization/reference	Year of publication	Population	Type of recommendation	Guidelines development process
Europe	European Academy of Pediatrics (EAP) [47]	2017	Infants Children Adolescents	■ RDAs and UIs ■ Supplementation for children at risk *Remarks: Evaluation of vitamin D status is justified in situations at risk for significant VDD.* *RDAs for children with risk factors for VDD are higher.*	Position statement.
Europe	European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [48]	2013	Infants Children Adolescents	■ 25(OH)D thresholds ■ UIs ■ Supplementation for children at risk	Position paper.
UK (England, Scotland, Wales, Ireland)	UK Department of Health [49]	2012	All ages	■ Supplementation doses for groups at risk	Public Health England published advice for health professionals. Recommendations for at risk groups.
	British Pediatric and Adolescent Bone Group [50]	2012	All ages	■ 25(OH)D thresholds ■ Supplementation for groups at risk	Position statement-Endorsement of the recommendations on supplementation published by the UK Department of Health.
	Royal College of Pediatrics and Child Health (RCPCH) [51]	2013	Infants Children Adolescents	■ 25(OH)D thresholds ■ Prevention doses ■ Treatment doses for VDD with symptoms *Remarks: Screen 25(OH)D in children with risk factors and symptoms or signs.* *In case of VDD, consider screening or treatment of family members.*	Practical interim guide for pediatricians.
	English Department of Health [52]	2016	All ages	■ Supplementation policy	Recommendations based on the 2016 SACN's findings. They targeted healthy population as well as groups at risk.
Central Europe	European study group [53]	2013	All ages	■ 25(OH)D thresholds ■ UIs ■ Supplementation doses ■ Treatment doses for VDD *Remarks: Screen 25(OH)D in patients at risk.*	European multidisciplinary working group elaborated consensus guidelines concerning the general population and groups at risk. Recommendations based on both skeletal and extra-skeletal effects of vitamin D.
France	French Pediatric Society [54]	2012	Infants Children Adolescents	■ 25(OH)D thresholds ■ Supplementation doses *Remarks: Screen 25(OH)D in certain pathological conditions.*	Committee on Nutrition established recommendations after summarizing scientific knowledge.
Germany Austria Switzerland (D-A-CH)	German Nutrition Society [55]	2012	All ages	■ 25(OH)D optimal level ■ AIs	Recommendations based on a review conducted by the German Nutrition Society and other published reviews and meta-analyses.
Switzerland	Federal Office of Public Health [56]	2012	All ages	■ 25(OH)D sufficient level ■ RDAs *Remarks: Patients at risk should turn to their doctor.*	Federal recommendations based on a report published by the Federal Food Commission and a national observational survey.
United Arabic Emirates and Gulf Countries	Study group [57]	2016	All ages	■ 25(OH)D recommended level ■ RDAs and UIs ■ Supplementation doses *Remarks:* *Screen 25(OH)D in patients at risk.*	Key opinion leaders developed guidelines for physicians. Reference on the 2011 IOM guidelines, the 2011 ES guidelines, and the 2013 guidelines for Central Europe.
India	Indian Academy of Pediatrics [58]	2017	Infants Children Adolescents	■ 25(OH)D thresholds ■ UIs ■ Supplementation doses for NR ■ Treatment doses for NR *Remarks: Screen 25(OH)D in children at risk.*	Committee of experts established a practice guideline for the prevention and treatment of VDD and calcium deficiency based on observational studies as well as on previous published recommendations.

Table 1
Continued

Country	Organization/reference	Year of publication	Population	Type of recommendation	Guidelines development process
Australia and New Zealand	Bone and Mineral Society and Osteoporosis [59]	2013	Infants Children Adolescents	■ 25(OH)D thresholds ■ RDAs ■ Treatment doses for children with VDD *Remarks: Screen 25(OH)D in children at risk together with calcium, phosphate and ALP levels.*	Position statement. Multidisciplinary working group developed guidelines based on articles on vitamin D dosing in pediatric ages groups.
U.S.	American Academy of Pediatrics (AAP) [60]	2008	Infants Children Adolescents	■ 25(OH)D target level ■ Supplementation approach *Remarks: Screen 25(OH)D in children at risk.*	Committee on Nutrition published recommendations about the prevention of rickets. Narrative overview of available data.
	American Academy of Pediatrics (AAP) [61]	2012	All ages	■ 25(OH)D sufficient level ■ AIs for infants, RDAs for all other ages UIs for all ages	Statement of endorsement of the 2011 IOM publication on DRIs for calcium and Vitamin D.

25(OH)D = 25-hydroxyvitamin D; AI = adequate intake; CF = Cystic Fibrosis; CKD = chronic kidney disease; DRI = dietary reference intake; DRV = dietary reference value; IOM = Institute of Medicine; NIH = National Institutes of Health; NR = nutritional rickets; RCT = randomized controlled trial; RDA = Recommended Dietary Allowance; RNI = Recommended Nutrient Intake; SACN =Scientific Advisory Committee on Nutrition; SI = safe intake; UI = upper intake; VDD = Vitamin D deficiency; WHO = World Health Organization.

D 25-hydroxyvitamin D (25(OH)D) is universally proposed as the best indicator of vitamin D status. There is clear lack of consensus in defining normal values for serum 25(OH)D concentration. This has given rise to a wide range of terminology to describe the status of vitamin D, including the terms "deficiency," "sufficiency," "insufficiency," "inadequacy," "adequacy," "optimal," "suboptimal" status, "target," and "recommended" level.

Deficiency is defined as a serum 25(OH)D concentration below 50 nmol/L according to eight societies (Endocrine Society [ES], SAHM, ESPN, Central Europe Study Group, Polish Society of Pediatric Endocrinology [PSPE], French Pediatric Society [FPS], IPS, and Australian Bone and Mineral Society and Osteoporosis) [31,34,39,40,45,53,54,59] or below 25–30 nmol/L according to six others (GC, British Bone Group, Royal College of Pediatrics and Child Health [RCPCH], AAP, Institute of Medicine [IOM], and AAP) [30,42,50,51,58,61].

A level below 25–30 nmol/L is considered as indicative of *severe deficiency* according to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition [48], the PSPE [39], the French Pediatric Society [54], and the IPS [40], whereas the half cutoff level (12.5 nmol/L) represents severe deficiency according to the Australian Bone and Mineral Society and Osteoporosis [59] and the ESPN [34].

The determination of *adequate* vitamin D status remains also controversial. For healthy populations, the most commonly accepted threshold (10 study groups) is that of the IOM [42], which sets this limit at concentrations equal or above 50 nmol/L. As a consequence, the term "*insufficiency*" has been introduced by certain societies [30,37,50,51,58,61] for serum 25(OH)D levels between 25–30 nmol/L and 50 nmol/L. Only two national committees, from the United Kingdom [36] and the Netherlands [38], use a more conservative level and consider that a serum 25(OH)D concentration as low as 25–30 nmol/L is sufficiently protective for the general population in terms of bone health. Higher cutoff values are proposed by six study groups (ES, SAHM, Central Europe Study Group, PSPE, IPS, and the Arabic-Gulf Countries) [31,39,40,45,53,57], which raise the definition of optimal status to levels higher than 75 nmol/L (usually 75–125 nmol/L), in order for individuals to maximize the effect of vitamin D on their bone and muscle metabolism as well as to benefit from its potential pleiotropic functions. These study groups consider the levels between 50 and 75 nmol/L as "*insufficient*" or "*suboptimal*." For chronic patients, certain societies recommend also higher 25(OH)D levels. For example, patients with CF [32] as well as those with CKD [34] are instructed to maintain their serum 25(OH)D concentration above 75 nmol/L. For NR, concentrations above 50 nmol/L are considered sufficient by two groups [30,58], whereas one other group sets sufficient status to levels higher than 75 nmol/L [40].

Dietary reference intakes for vitamin D

We identified 22 reports [30,31,33,36–44,46–48,53,55–59,61] on nutritional intakes for vitamin D in adolescents (Table 3).

No true consensus emerges from these documents. Recommendations for adequate nutritional requirements for healthy adolescents vary between 200 IU/d and 1,000 IU/d.

The majority of study groups are based on the "Recommended Dietary Allowance." This is defined as the amount of vitamin D deemed adequate to meet the nutritional needs of

Table 2
Thresholds of serum 25(OH)D in adolescents

Country	Organization/reference	Year of publication	Population	25(OH)D thresholds (nmol/L[a])
Global	Consensus of 11 societies [30]	2016	All ages	Intoxication >250 nmol/L[b] Sufficiency >50 nmol/L Insufficiency 30–50 nmol/L Deficiency <30 nmol/L
Global	Endocrine Society [31]	2011	All ages	Sufficiency >75 nmol/L Insufficiency 50–75 nmol/L Deficiency ≤ 50 nmol/L
Global	Society for Adolescent Health and Medicine (SAHM) [45]	2013	Adolescents	Intoxication >250 nmol/L[b] Optimal level 75–125 nmol/L Sufficiency >75 nmol/L Insufficiency 50–75 nmol/L Deficiency ≤ 50 nmol/L
Global	Cystic Fibrosis Foundation [32]	2012	All patients with CF	Optimal level 75–125 nmol/L
Europe	European Panel on Dietetic Products, Nutrition and Allergies [33]	2016	All ages	Target value 50 nmol/L
Europe	European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [48]	2013	Children	Sufficiency >50 nmol/L Severe deficiency <25 nmol/L
Europe	European Society of Pediatric Nephrology (ESPN) [34]	2017	All children with CKD	Intoxication >250 nmol/L[b] Sufficiency >75 nmol/L Insufficiency 50–75 nmol/L Deficiency 12–50 nmol/L Severe deficiency <12 nmol/L
UK (England, Scotland, Wales, Ireland)	British Pediatric and Adolescent Bone Group [50]	2012	All ages	Sufficiency >50 nmol/L Insufficiency 25–50 nmol/L Deficiency <25 nmol/L
	Royal College of Pediatrics and Child Health (RCPCH) [51]	2013	All ages	Sufficiency >50 nmol/L Insufficiency 25–50 nmol/L Deficiency <25 nmol/L
	Scientific Advisory Committee on Nutrition (SACN) [36]	2016	All ages	Protective level ≥ 25 nmol/L
Nordic Countries	Nordic Council of Ministers [37]	2012	All ages	Sufficiency >50 nmol/L Insufficiency 30–50 nmol/L
The Netherlands	Health Council of the Netherlands [38]	2012	All ages	Target level ≥ 30 nmol/L
Central Europe	European study group [53]	2013	All ages	Toxic level >500 nmol/L Risky level >250 nmol/L High supply 125–250 nmol/L Target level 75–125 nmol/L Suboptimal level 50–75 nmol/L Deficiency <50 nmol/L
Poland	Polish Society of Pediatric Endocrinology and Diabetes and Expert Panel [39]	2018	All ages	Toxic level >250 nmol/L High supply 125–250 nmol/L Optimal level 75–125 nmol/L Suboptimal level 50–75 nmol/L Deficiency 25–50 nmol/L Severe deficiency ≤ 25 nmol/L
France	French Paediatric Society [54]	2012	All ages	Moderate deficiency 30–50 nmol/L Severe deficiency <30 nmol/L
D-A-CH (Germany, Austria, Switzerland)	German Nutrition Society [55]	2012	All ages	Optimal level ≥ 50 nmol/L
Switzerland	Federal Office of Public Health [56]	2012	All ages	Sufficiency ≥ 50 nmol/L
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Children	Sufficiency ≥ 75 nmol/L Insufficiency 50–74 nmol/L Deficiency <50 nmol/L Severe deficiency <25 nmol/L
United Arabic Emirates and Gulf Countries	Study group [57]	2016	All ages	Recommended level 75–150 nmol/L

Table 2
Continued

Country	Organization/reference	Year of publication	Population	25(OH)D thresholds (nmol/L[a])
India	Indian Academy of Pediatrics [58]	2017	Children	Intoxication >250 nmol/L[b] Sufficiency >50 nmol/L Insufficiency 30–50 nmol/L Deficiency <30 nmol/L
Australia and New Zealand	Bone and Mineral Society and Osteoporosis [59]	2013	Children	Elevated level >250 nmol/L Sufficiency ≥ 50 nmol/L Mild deficiency 30–49 nmol/L Moderate deficiency 12.5–29 nmol/L Severe deficiency <12.5 nmol/L
U.S. and Canada	Institute of Medicine [42]	2011	All ages	Sufficiency ≥ 50 nmol/L Inadequacy 30–50 nmol/L Deficiency <30 nmol/L
U.S.	American Academy of Pediatrics (AAP) [61]	2012	All ages	Sufficiency ≥ 50 nmol/L Inadequacy 30–50 nmol/L Deficiency <30 nmol/L

25(OH)D = 25-hydroxyvitamin D; CF = Cystic Fibrosis; CKD = chronic kidney disease.
[a] For the serum 25(OH)D concentration consider: 1 nmol/L = .4 ng/mL or alternatively 1 ng/mL = 2.5 nmol/L.
[b] For the definition of vitamin D toxicity consider as necessary: 25(OH)D > 250 nmol/L and hypercalcemia with hypercalciuria and suppressed PTH.

almost all subjects (97.5% of the population) to obtain a sufficient vitamin D status when exposure to ultraviolet B radiation is zero or minimal. The term "adequate intake" has also been established when evidence is insufficient to develop a Recommended Dietary Allowance and is set at a level assumed to ensure nutritional adequacy.

As a consequence, most guidelines (10 reports) [30,31,33,42,44,47,56,58,59,61] propose a daily intake of 600 IU in accordance with the generally accepted 25(OH)D serum threshold of at least 50 nmol/L. The Coordinated Nutrition Society for Germany, Switzerland, and Austria (D-A-CH) [55] recommends 800 IU/d to achieve a serum 25(OH)D concentration of 50 nmol/L. Higher intakes of up to 1,000 IU/d are recommended by the ES [31], which considers a higher optimal level of 25(OH)D (>75 nmol/L). The United Kingdom [36] and the Netherlands [38] suggest lower nutrient values, that is, 400 IU/d, consistent with the lower protective value of 25(OH)D that they recommend (25–30 nmol/L). The World Health Organization [43] and the Australian Ministry of Health [41] propose an even lower level (200 IU/d).

Five documents (ES, International Expert Group, EAP, Nordic Countries, and Arabic-Gulf Countries) [31,37,44,47,57] provide specific consideration regarding nutritional requirements for adolescents at risk for VDD. According to these recommendations, dietary intakes in vitamin D for adolescents with risk factors should be higher than the common intakes for healthy adolescents, that is, about 800–1,000 IU/d.

As far as the tolerable upper intake level (UL) is concerned, there are limited data on toxic doses of vitamin D in adolescent populations. The UL reported by the IOM in 2011 [42] and verified by the European Panel on Dietetic Products in 2012 [46] is commonly endorsed by all study groups (13 references) [31,37–40,42,46–48,53,57,58,61], except for the Australian Ministry of Health. A daily intake of 4,000 IU is defined as the UL for adolescents, identical to the UL for adults. This dose represents less than half the daily dose for which no adverse effect is observed, estimated for adults at 10,000 IU/d.

Prophylactic vitamin D supplementation

We found 18 documents [30,35,38–40,44,45,47–54,57,58,60] concerning vitamin D supplementation in adolescents (Table 4).

There is good agreement on the need for a daily preventive dose for all adolescents at risk of VDD, such as those with chronic medical conditions, which affect vitamin D absorption, metabolism, and storage, as well as those with dark skin or minimal sun exposure. However, prophylactic doses are debated, ranging from doses equal to the relevant recommended dietary intake, to doses that are significantly higher. For example, in England [35,49–52] and the Netherlands [38], adolescents at risk for VDD are instructed to take a daily 400 IU supplement. The International Expert Group [44], SAHM [45], the RCPCH [51], the IPS [40], and the IAP [58] recommend daily supplementation doses up to 1,000 IU for adolescents at risk. The PSPE [39] suggests even higher preventive doses, that is, 2,000 IU/d, for at-risk adolescents. Six study groups [39,40,44,53,57,58] make a specific recommendation regarding supplementation in obese adolescents. The suggested daily prophylactic dose varies between 1,000 IU and 4,000.

On the other hand, there is lack of consensus regarding the need to supplement healthy adolescents. In such a case, the

Table 3
Dietary reference intakes for vitamin D in adolescents

Country	Organization/reference	Year of publication	Population	Dietary reference intake (IU/d[a])		
				RDA	AI	UI
Global	World Health Organization (WHO) jointly with the Food and Agriculture Organization of the United Nations [43]	2004	Children aged 0–18 y and adults aged 19–50 y	200		
Global	Consensus of 11 societies [30]	2016	Children aged 1–18 y and adults	600		
Global	International Expert Group [44]	2015	Children and adolescents aged 1–18 y	600[b]		
Global	Endocrine Society [31]	2011	Children and adolescents aged 1–18 y	600[c]		4,000
Europe	European Panel on Dietetic Products, Nutrition and Allergies [33, 46]	2012 2016	Adolescents aged 11–17 y and adults Children aged 1–17 y and adults		600	4,000
Europe	European Academy of Pediatrics (EAP) [47]	2017	Adolescents aged 11–17 y	600[d]		4,000
Europe	European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [48]	2013	Adolescents aged 11–17 y			4,000
UK (England, Scotland, Wales, and Ireland)	Scientific Advisory Committee on Nutrition (SACN) [36]	2016	Children aged 4–18 y and adults	400		
Nordic Countries	Nordic Council of Ministers [37]	2012	Children aged 11–17 y and adults aged 18–74 y	400[e]		4,000
The Netherlands	Health Council of the Netherlands [38]	2012	Children aged 11–17 y and adults aged 18–70 y		400	4,000
Central Europe	European study group [53]	2013	Adolescents aged 11–18 y and adults			4,000
Poland	Polish Society of Pediatric Endocrinology and Diabetes and Expert Panel [39]	2018	Adolescents aged 11–18 y			4,000
D-A-CH (Germany, Austria, Switzerland)	German Nutrition Society [55]	2012	Children aged 1–18 y and adults		800	
Switzerland	Federal Office of Public Health [56]	2012	Children aged 2–18 y and adults aged 19–60 y	600		
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Adolescents aged 11–17 y			4,000
United Arabic Emirates and Gulf Countries	Study group [57]	2016	Adolescents aged 11–18 y	600–1,000[f]		4,000
India	Indian Academy of Pediatrics [58]	2017	Children aged 9–18 y		600	4,000
Australia and New Zealand	Ministry of Health [41] Bone and Mineral Society and Osteoporosis [59]	2006 2013	Children aged 1–18 y and adults 19–50 y Children and adolescents aged 1–18 y	600	200	3,200
U.S. and Canada	Institute of Medicine [42]	2011	Children aged 9–18 y and adults aged 19–70 y	600		4,000
U.S.	American Academy of Pediatrics (AAP) [61]	2012	Children aged 9–18 y and adults 19–70 y	600		4,000

AI = adequate intake; RDA = Recommended Dietary Allowance; UI = upper intake.

[a] For the dietary intake of cholecalciferol (D3) or ergocalciferol (D2) consider: 1 IU/d = .025 μg or alternatively 1 μg = 40 IU.

[b] For children with risk factors consider 600–1,000 UI/d. Obese children and children on anticonvulsant medications, glucocorticoids, or antifungals should receive at least two to three times more vitamin D.

[c] 1,000 IU/d to raise 25(OH)D level above 75 nmol/L. Obese patients and patients on anticonvulsant medications, glucocorticoids, antifungals, and medication for AIDS should be given at least two to three times more vitamin D.

[d] Intakes for children with risk factors of VDD are higher.

[e] 800 IU/d for people with little or no sun exposure.

[f] RDA depends on body weight and season.

Table 4
Recommendations for prophylactic supplementation with vitamin D in adolescents

Country	Organization/reference	Year of publication	Population	Recommendation	Risk for VDD definition
Global	Consensus of 11 societies [30]	2016	Children aged 1–18 y and adults	Groups *at risk* in the absence of food fortification	• History of symptomatic VDD requiring treatment • Factors or conditions that reduce synthesis or intake of vitamin D • Pregnancy
Global	International Expert Group [44]	2015	Children and adolescents aged 2–18 y	■ No risk factors but limited summer sun exposure: 600 IU/d in the late fall and winter ■ *Risk factors:* 600–1,000 UI/d all year around *Remarks: Children who are obese or on specific medications[a] should receive at least two to three times more vitamin D*	
Global	Society for Adolescent Health and Medicine (SAHM) [45]	2013	Adolescents	■ *No risk factors:* 600 IU/d all year around ■ *Risk factors:* 1,000 IU/d all year around *Remarks: Supplement with a vitamin D3 preparation*	• Increased skin pigmentation • Frequent use of sunscreen • Obesity • Specific diets (vegan/macrobiotic) • Cultural convention associated with body coverage • Malabsorption • Amenorrhea • Pregnancy or lactation • Immobilization • Following bariatric surgery • Chronic kidney disease • Chronic liver disease • Medications[b] • Recurrent fractures or known low bone mineral density status
Europe	European Academy of Pediatrics (EAP) [47]	2017	Children and adolescents aged 1–18 y	Consider supplementation in children *at risk*	• Dark skin • Areas with reduced sun exposure • Chronic liver/kidney disease • Malabsorption • Dietary inadequacy • Inflammatory bowel disease • Long-term parenteral nutrition • Institutionalized children • Anticonvulsant medications
Europe	European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [48]	2013	Children aged 1–18 y	Consider supplementation in children *at risk*	• Dark skin living in northern countries • Inadequate sun exposure[c] • Obesity
UK	UK Department of Health [49]	2012	Children aged 5–18 y and adults	400 IU/d in groups *at risk*	• Pregnancy/breastfeeding • Limited sun exposure • Dark skin
	British Pediatric and Adolescent Bone Group [50]	2012	Children aged 5–18 y and adults	400 IU/d in groups *at risk*	• Pregnancy/breastfeeding
	College of Pediatrics and Child Health (RCPCH) [51]	2013	Children aged 1–18 y	400–1,000 UI/d in children with *risk factors* Consider prevention dose in children without risk factors	• Increased need (adolescence, obesity, pregnancy/breastfeeding) • Reduced sun exposure[d] • Limited diet[e]

(*continued on next page*)

Table 4
Continued

Country	Organization/reference	Year of publication	Population	Recommendation	Risk for VDD definition
	National Institute for Health and Care Excellence (NICE) [35]	2014	All ages	*At-risk* groups are advised to take a supplement that meets 100% of the agreed RNI for their age group.	• Pregnancy/breastfeeding • Low or no sun exposure • Dark skin
	English Department of Health [52]	2016	Children aged 1–18 y and adults	■ *No risk factors:* 400 IU/d in autumn and winter ■ *Risk factors:* 400 IU/d all year around	• Little or no sun exposure • Dark skin
The Netherlands	Health Council of the Netherlands [38]	2012	Children aged 4–18 y and adults aged 19–50 y	400 IU/d in groups *at risk*	• Dark skin • Fair skin and insufficient sun exposure[f]
Central Europe	European study group [53]	2013	Children and adolescents aged 1–18 y	■ *No risk factors:* 600–1,000 IU/d between September and April (dose depending on body weight) ■ *No risk factors but insufficient summer sun exposure:* 600–1,000 IU/d all year around (dose depending on body weight) ■ *Obesity:* 1,200–2,000 IU/d (depending on severity of obesity) *Remarks: Pregnancy: 1,500–2,000 IU/d*	• Obesity
Poland	Polish Society of Pediatric Endocrinology and Diabetes and Expert Panel [39]	2018	Adolescents aged 11–18 y	■ *No risk factor but insufficient summer sun exposure*[g]: 800–2,000 IU/d all year around (dose depends on body weight and dietary vitamin D intake) ■ *Risk factors:* 2,000 IU/d all year around if 25(OH)D testing not possible ■ *Obesity:* 1,600–4,000 IU/d *Remarks: Before supplementation, the probability of vitamin D hypersensitivity should be assessed if feasible* *Ensure a sufficient calcium intake during vitamin D supplementation*	• Locomotor diseases • Calcium/phosphorus metabolism diseases • Medications • Malabsorption/maldigestion • Liver/kidney disease • Endocrine disorders • Somatic development disorders • Developmental delay • Nervous system diseases • Allergies • Autoimmune/immune disorders • Cardiovascular diseases • Metabolic disorders • Neoplasms • Obesity
France	French Pediatric Society [54]	2012	Adolescents aged 10–18 y	■ *No risk factors:* 2 doses of 80,000–100,000 IU on November and February Consider 1 single dose of 200,000 IU in winter for compliance reasons ■ *Risk factors:* 80,000–100,000 IU every 3 months all year around	• Dark skin • Sun exposure factors[h] • Malabsorption, cholestasis, kidney failure, nephritic syndrome • Drugs[i] • Obesity • Extreme diets (veganism)
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Children and adolescents 1–18 y	■ No risk factors but reduced summer sun exposure: 600 IU/d between November and April ■ *Risk factors:* 600–1,000[j] IU/d all year around Consider intermittent dosing (weekly or monthly) for a cumulative monthly dose of 18,000–30,000 IU in cases of poor compliance particularly during adolescence *Remarks: Children on certain drugs*[k] *should receive at least two to three*	• Dark skin • Reduced sun exposure[l] and/or constant use of sunscreens • International adoption • Inadequate diets (i.e., vegan diet) • Chronic kidney disease • Hepatic failure/cholestasis • Malabsorption • Drugs[k]

Table 4
Continued

Country	Organization/reference	Year of publication	Population	Recommendation	Risk for VDD definition
				times more vitamin D *Obese children should receive higher dose (1,000–1,500 IU/d)*	
United Arabic Emirates and Gulf Countries	Study group [57]	2016	Children and adolescents aged 1–18 y	■ *No risk factors:* 600–1,000 IU/d between May and October (dose depends on body weight) ■ *No risk factors but insufficient winter sun exposure:* 600–1,000 IU/d all year around (dose depends on body weight) ■ *Obesity:* 1,200–2,000 IU/d (depending on severity of obesity) *Remarks:* *Pregnancy: 1,500–2,000 IU/d*	• Obesity
India	Indian Academy of Pediatrics [58]	2017	Children and adolescents aged 1–18 y	■ *No risk factors:* 600 IU/d all year around ■ *Risk factors:* 600–1,000 IU/d all year around ■ *Obesity:* two to three times higher doses *Remarks: Adequate calcium intake (600–800 mg/d) should be ensured*	• Dark skin • Areas with reduced sun exposure • Malabsorption • Chronic liver/kidney disease • Transplant recipients • Anti-seizure medications • Malignancy treatment • Restricted sun exposure • History of rickets • Predisposition to osteoporosis • Obesity
U.S.	American Academy of Pediatrics (AAP) [60]	2008	Adolescents	■ *If limited dietary intake of vitamin D*[m]: 400 IU/d *Remarks: Consider higher supplementation doses in children at risk*	• Increased skin pigmentation • Decreased sunlight exposure • Fat malabsorption • Anticonvulsant medications

25(OH)D = 25-hydroxyvitamin D; RNI = recommended nutrient intake; VDD = vitamin D deficiency.
[a] Medications: anticonvulsant medications, glucocorticoids, or antifungals.
[b] Medications: glucocorticoids, anticonvulsants, and HIV medications.
[c] Inadequate sun exposure: excessive use of sunscreen with high SPF, staying indoors for much of the day, wearing clothes covering most of the skin, living in northern latitudes during wintertime.
[d] Reduced sun exposure: northern latitude (above 50°), season (winter and spring), dark skin, wearing concealing clothing, immobility, excessive use of sun.
[e] Limited diet: vegetarians/vegans, exclusion diets, malabsorption, liver disease, renal disease, drugs (e.g., anticonvulsants, anti-TB drugs).
[f] Insufficient exposure to sunlight: not ensuring a maximum exposure of 15–30 minutes to the sun between 11 and 15 hours (head and hands exposed).
[g] Insufficient summer sun exposure: adolescents not sunbathing with uncovered forearms and legs for at least 15 minutes between 10 and 15 hours without sunscreen in the period from May to September.
[h] Sun exposure factors: absence of summer sun exposure, dermatologic condition preventing such exposure, wearing skin-concealing clothing in summer.
[i] Drugs: rifampicin, antiepileptics (phenobarbital, phenytoin).
[j] 1,000 IU/d for children and adolescents with multiple risk factors for VDD.
[k] Drugs: anticonvulsants, oral glucocorticoids, systemic antifungals, and antiretroviral drugs.
[l] Reduced sun exposure because of lifestyle factors, chronic illness or hospitalization, complex disability, institutionalization, covering clothing for religious, or cultural reasons.
[m] Limited dietary vitamin D intake: adolescents who do not obtain 400 IU of vitamin D per day through vitamin D–fortified food.

optimal dose, season, and duration of supplementation remain debated. In general, the recommended daily doses range between 400 IU and 2,000 IU, depending on sun exposure, consumption of vitamin D fortified foods, and body weight.

More precisely, when seasonal concerns are taken into consideration when prescribing supplementation, all healthy adolescents living in England [52], Central Europe [53], or France [54] are instructed to take vitamin D supplements in the autumn and winter period, whatever their exposure to sunlight in the summer. Scientists in the Arab States of the Gulf recommend that supplementation be carried out in summer months [57]. Daily regimens vary considerably (400–1,000 IU), depending also on body weight. In France, to favor adherence, a single dose of 200,000 IU during winter is recommended. Two study groups (GC and IPS) [30,40] favor supplementing healthy adolescents with a daily dose of 600 IU in the autumn and winter if summer sun exposure is limited.

As far as continuous supplementation in healthy adolescents throughout the whole year is concerned, SAHM [45] and the IAP [58] recommend a daily vitamin D supplement of 600 IU taking into consideration teenagers' lifestyle. The AAP [60] recommends a daily supplement of vitamin D containing 400 IU all year around for all adolescents who do not consume vitamin D–fortified foods. When summer sun exposure is taken into account, adolescents living in Poland [39], Central Europe [53], or the Arabic-Gulf Countries [57] are instructed to receive a daily supplement of 600–2,000 IU (dose depending on body weight) all year around if sufficient exposure to the sunlight is not ensured during summer months.

Treatment of VDD

We identified 11 reports [30–32,34,39,40,45,51,53,58,59] about the management of VDD and insufficiency in adolescents (Table 5).

Different committees recommend different treatment doses, depending on the presence of illness and/or the serum 25(OH)D level obtained at baseline. Oral vitamin D treatment is most commonly recommended. There are two different oral formulations, ergocalciferol or D2 and cholecalciferol or D3. SAHM and the CFF declare specific preference for D3 preparations over D2.

The GC [30] and the IAP [58] provided recommendations about the treatment of NR. The IPS [40] established guidelines for both NR and asymptomatic VDD. The RCPCH [51] developed recommendations for the treatment of symptomatic VDD. Two societies focused on management of the VDD in specific medical conditions (CF and CKD) [32,34]. The remaining five study groups [31,39,45,53,59] developed recommendations for VDD and/or insufficiency with no specific considerations in relation to the presence of clinical signs/symptoms.

For the treatment of NR, a daily dose of 3,000–6,000 IU/d is recommended, depending on the age of the adolescent [30,40,58]. There is agreement on the need for prolonged treatment, that is, at least 3 months. Large doses in a weekly (50,000–60,000 IU per week for 6–8 weeks) [40,58] or monthly (100,000 IU per month for 3–4 months) [40] basis or even single loading doses (up to 300,000 IU) [30] are also suggested to favor adherence. For the treatment of symptomatic VDD in adolescents aged >12 years, the RCPCH recommends higher daily doses, equal to 10,000 IU/d for 4–8 weeks, or even single bolus doses (300,000 IU) [51]. In cases of both NR and symptomatic VDD, ensuring an adequate daily calcium intake is also suggested, with variable dosing.

For the treatment of insufficiency, an increase in the prophylactic dose is usually recommended [32,34,39,45,53]. For the treatment of deficiency, different regimens have been proposed. For adolescents with chronic diseases (CKD or CF), therapeutic doses are high and can reach up to 8,000 IUD or 10,000 IU/d, respectively [32,34]. For healthy adolescents with VDD, daily treatment doses vary considerably, between 1,000 and 5,000 IU [31,39,53,59]. The duration of daily treatment is not universally determined and varies between 1 and 3 months. Alternatively, higher doses in a weekly (50,000 IU per week for 6–8 weeks) basis have also been proposed by SAHM [45]. Loading doses, that is, a single dose of 150,000 IU or two doses of 150,000 IU at a 6-week interval, depending on the baseline serum 25(OH)D concentration, have also been recommended in Australia [59]. However, certain study groups [34,39,40,53] express concerns about administering bolus doses, especially doses larger than 300,000 IU.

The ES [31] and the IPS [40] suggest that adolescents on certain medications that affect vitamin D metabolism as well as obese adolescents require a higher therapeutic dose, that is, at least two to three times higher than the recommended dosing for healthy individuals.

There is general agreement on the need for a maintenance dose after the end of the main course of treatment to maintain adequate serum 25(OH)D levels. The maintenance regime varies between 400 and 2,000 IU and is usually equivalent to the daily dietary intake recommended by the relevant study group.

Discussion

The main finding of this study is a global lack of consensus about the identification, prevention, and management of VDD in adolescence.

Our synthesis demonstrates lack of consensus among countries about the optimal status and adequate nutritional requirements. Controversy also remains about the need for prophylactic supplementation in healthy adolescents. On the other hand, there is good general agreement about supplementing all adolescents at risk; however, the dose is debated. Adequate long-term treatment of VDD followed by maintenance treatment is commonly accepted, yet, the proposed therapeutic regimens vary significantly.

Strengths and limitations

To our knowledge, this is the first review focusing on all aspects of vitamin D in adolescence. We assembled all available guidelines and structured them thematically in a more coherent and comprehensive way. A major force of our review is the use of both scientific databases and gray literature. This systematic approach allowed us to consider recommendations developed by scientific societies as well as government publications and to reduce the likelihood of missing important sources.

Our work also has weaknesses. First, we took into consideration reports targeting adolescents but also reports that address a wide range of age groups (infants, children, and adults). In most published documents, there was no clear distinction for specific data about the adolescent subgroup. Adolescents have great mineral demands because of their growing skeleton, and therefore, particular criteria should apply when developing guidelines

Table 5
Recommendations for treatment of vitamin D deficiency/insufficiency in adolescents

Country	Organization/reference	Year of publication	Population	25(OH)D treatment cut-off level (nmol/L)	Recommendation
Treatment of NR					
Global	Consensus of 11 societies [30]	2016	Children and adolescents aged 1–12 y with NR Adolescents aged >12 y with NR	Diagnosis of NR is based on history, physical examination, and biochemical testing, and confirmed by radiographs.	Prescribe 3,000–6,000 IU/d for at least 3 m or a single dose of 150,000 IU *Maintenance*: 600 IU/d Prescribe 6,000 IU/d for at least 3 m or a single dose of 300,000 IU *Maintenance*: 600 IU/d *Remarks: ensure a daily calcium intake of at least 500* mg (dietary intake or supplements)
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Children and adolescents aged 1–12 y with NR Adolescents aged 13–18 y with NR	Diagnosis of NR is based on clinical, biochemical, and radiologic findings.	3,000–6,000 IU/d for 3 m *Maintenance*: 600–1,000 IU/d 6,000 IU/d for 3 m or 50,000 IU/w for 6–8 w or 100,000 IU/m for 3–4 m *Maintenance*: 600–1,000 IU/d *Remarks: A single large dose of >300,000 IU is not recommended* *Administer a daily calcium intake of 30–75 mg/kg in 3 divided doses*
India	Indian Academy of Pediatrics [58]	2017	Children and adolescents aged 1–18 y with NR		3,000–6,000 IU/d for 3 m or 60,000 IU/w for 6 w *Maintenance*: 600 IU/d *Remarks: ensure a daily calcium intake of 600–800 mg*
Treatment of symptomatic VDD					
UK	Royal College of Pediatrics and Child Health (RCPCH) [51]	2013	Children and adolescents aged 6 mo–12 y with symptomatic VDD Adolescents aged 12–18 y with symptomatic VDD	<25	Prescribe 6,000 IU/d for 4–8 w *Maintenance:* prevention dose until growth completion Prescribe 10,000/d for 4–8 w A single dose (multiply daily dose by 30) is recommended if compliance concerns *Maintenance:* a prevention dose should follow the treatment dose until growth completion *Remarks: ensure a sufficient dietary calcium intake*
Treatment of asymptomatic VDD					
Italy	Italian Pediatric Society Italian Society of Preventive and Social Pediatrics Italian Federation of Pediatricians [40]	2018	Adolescents with asymptomatic VDD	<75	• If 25(OH)D = 50–74 nmol/L: prescribe prophylactic dose • If 25(OH)D <50 nmol/L: prescribe 2,000 IU/d or 50,000/w for 8 w *Maintenance*: 600–1,000 IU/d *Remarks: obese adolescents require higher treatment doses, i.e., 2,000–4,000 IU/d* *Adolescents on certain medications should receive higher treatment dose, at least 2,000–4,000 IU/d*

(*continued on next page*)

Table 5
Continued

Country	Organization/reference	Year of publication	Population	25(OH)D treatment cut-off level (nmol/L)	Recommendation
Treatment of VDD or insufficiency					
Global	Endocrine Society [31]	2011	Children aged 1–18 y	<50	Prescribe 2,000 IU/d or 50,000 IU/w for at least 6 w *Maintenance:* 600–1,000 IU/d *Remarks: For children with obesity, malabsorption syndromes or on medications affecting vitamin D metabolism, prescribe a higher dose (two to three times higher)*
Global	Society for Adolescent Health and Medicine (SAHM) [45]	2013	Adolescents	<75	• If 25(OH)D = 50–75 nmol/L: prescribe 1,000 IU/d for a minimum of 3 m • If 25(OH)D <50 nmol/L: prescribe 50,000 IU/w for 8 w Intermittent high doses every 2–3 months could also be considered for adherence reasons. *Maintenance:* 1,000 IU/d *Remarks: treat with a vitamin D3 preparation*
Global	Cystic Fibrosis Foundation [32]	2012	Children aged >10 y and adults with CF	<75	• Initial dose: 800–2,000 IU/d • If 25(OH)D = 50–75 nmol/L: increase to 1,600–6,000 IU/d • If 25(OH)D <50 nmol/L: increase to max 10,000 IU/d *Remarks: cholecalciferol D3 should be preferred over ergocalciferol D2*
Europe	European Society of Pediatric Nephrology (ESPN) [34]	2017	Children and adolescents aged 1–18 y with CKD and on dialysis	<75	• If 25(OH)D = 50–75 nmol/L: prescribe 2,000 IU/d • If 25(OH)D = 12–50 nmol/L: prescribe 4,000 IU/d • If 25(OH)D <12 nmol/L: prescribe 8,000 IU/d *Maintenance*: 1,000–2,000 IU/d *Remarks: Mega-dose vitamin D therapy is not recommended* *Measure serum Ca and urinary Ca levels 1–3 monthly based on CKD stage*
Central Europe	European study group [53]	2013	Children and adolescents aged 1–18 y	<75	• If 25(OH)D = 50–75 nmol/L: increase the prophylactic dose • If 25(OH)D <50 nmol/L: prescribe 3,000–5,000 IU/d (depending on body weight) for 1–3 m *Remarks: loading doses of >300,000 IU are not recommended*

Table 5
Continued

Country	Organization/reference	Year of publication	Population	25(OH)D treatment cut-off level (nmol/L)	Recommendation
Poland	Polish Society of Pediatric Endocrinology and Diabetes and Expert Panel [39]	2018	Children aged >10 y	<75	• If 25(OH)D = 50–75 nmol/L: increase the supplementation dose by 50% if vitamin D was previously prescribed or start supplementation if not the case. Measure 25(OH) in 6-month time • If 25(OH)D = 25–50 nmol/L: increase the supplementation dose by 100% if vitamin D was previously prescribed or start supplementation at maximal doses if not the case. Measure 25(OH) in 3-month time • If 25(OH)D <25 nmol/L: prescribe 6,000 IU/d for 3 m. Measure 25(OH) in 1–3-month time *Remarks: A single loading dose is not recommended* *Ensure a sufficient calcium intake*
Australia and New Zealand	Bone and Mineral Society and Osteoporosis [59]	2013	Children and adolescents aged 1–18 y	<50	• If 25(OH)D = 30–50 nmol/L: prescribe 1,000–2,000 IU/d for 3 m or a single dose of 150,000 IU • If 25(OH)D <30 nmol/L: prescribe 1,000–2,000 IU/d for 6 m or prescribe 3,000–4,000 IU/d for 3 m or prescribe two doses of 150,000 IU at a 6-week interval *Maintenance:* 400 IU/d or 150,000 IU at start of autumn

25(OH)D = 25-hydroxyvitamin D; CF = cystic fibrosis; CKD = chronic kidney disease; NR = nutritional rickets; VDD = vitamin D deficiency.

for this population. Second, linguistic bias probably influences our results. Efforts to identify and evaluate documents published in languages other than English or French are needed to better understand the different strategies existing around the world. Finally, we included three reports focusing on populations with chronic diseases (CF, CKD, and NR). These recommendations should not extend beyond these specific populations and cannot be generalized to all adolescents.

Implications for research: the need for a stronger evidence base

Only one third of published documents provided a description of the guidelines development process. In particular, most of the study groups did not use transparent and explicit methods to evaluate the best available evidence, instead they provided position statements of endorsement of previously published guidance or established guidelines based on experts' opinion. Therefore, most of the guidelines did not adhere to the formal standards regarding recommendations development processes. Besides, even study groups that used reliable systems for grading the evidence were unable to establish strong recommendations because of lack of high-quality data.

In addition, serum 25(OH)D cutoff levels proposed by different organizations were mostly based on results from studies involving adults. This kind of studies uses a variety of criteria to define the adequacy of vitamin D, such as suppression of the parathyroid hormone, maximum intestinal absorption of calcium, and bone mineral density. Information on relationships between 25(OH)D levels and functional outcome measures in children and adolescents is lacking [42]. However, the generalization of findings, which are in any case inconsistent, from adult to adolescent populations is not always appropriate, especially when targeting bone outcomes during adolescence, a period of maximum growth and bone mass attainment. This, also, helps understanding the reason why different study groups come up with different views about cutoff levels, and consequently, the need to supplement/treat or not. Moreover, the use of the clinical criterion of disease (rickets) appearance to define VDD is not unique when other bone pathologies could also emerge. For example, subclinical deficiency during adolescence may exacerbate bone remodeling and increase the risk of osteopenia or osteoporosis [2].

Some recommendations for vitamin D supplementation during adolescence were based on observational studies reporting an inadequate dietary intake of vitamin D [18,62,63] and an inadequate endogenous synthesis because of lack of dietary intake or sun exposure. However, the recommended dose of supplementation remains controversial. So far, there is only one systematic review and meta-analysis of six trials that examined the effect of vitamin D supplementation on bone density in children and adolescents [64]. Overall, it seems that supplementation does not have significant effects on bone health in healthy children with normal vitamin D levels but may have clinically useful benefits for peak bone mass, mostly in children with a baseline serum 25(OH)D concentration lower than 35 nmol/L. However, this remains to be clearly demonstrated.

Implications for practice: favoring pragmatic approaches while awaiting further evidence

Although most recommendations imply monitoring vitamin D status in groups at risk for VDD, it seems reasonable also to consider practices that favor a reduction in the volume of 25(OH)D testing [65]. In France, for example, laboratory 25(OH)D measurements before supplementation remain rigidly restricted to adolescents with well-defined severe medical conditions, and supplementation without prior testing is recommended for all other adolescents [66]. The same approach is proposed in the United Kingdom where vitamin D status testing is justified only in the presence of symptoms or signs of deficiency [35,51]. SAHM recommends that, if a 25(OH)D measurement cannot be obtained, youth with increased skin pigmentation, adolescents who use sunscreens frequently as well as obese teenagers should empirically receive a daily supplement of 1,000 IU [45]. The argument could be made to supplement systematically all at-risk adolescents and forego laboratory testing taking into account that vitamin D is relatively safe and cheap. Such an approach could reduce the prevalence of VDD and limit inconvenience and costs associated with monitoring and treating [28,29]. Nevertheless, dose–response studies need to be undertaken in adolescents to determine both the effective dose and the long-term safety of continuous supplementation.

Concerns about administrating large bolus doses [34,39,40,53] or even the necessity of genetic testing when prescribing vitamin D [40] have been expressed by certain authors. Vitamin D excess seems to be infrequent and asymptomatic. Adverse event analysis has identified increased hypercalcemia risk with cumulative doses above 400,000 IU in infants, but it remains unanswered whether the potentially toxic doses for adolescents have to be considered equal or rather higher [67]. Rare genetic defects may lead to the syndrome of idiopathic infantile hypercalcemia, which is associated with hypersensitivity to vitamin D even when administration is within commonly recommended doses [68]. These considerations may not seem justified when speaking about teenagers as it is unusual for children with familial or renal defects to remain undiagnosed until adolescence.

The IOM considers that the prevalence of VDD has been overestimated because of the use of inappropriately high cutoff points [69]. Because of the publication of the IOM report [42] in 2011 followed by the ES publication [31] in the same year, there is an ongoing debate about the optimal vitamin D status and the relevant dietary requirements. The major difference between the two committees is the fact that the IOM developed guidelines for the entire healthy population, whereas the ES established clinical recommendations with an emphasis on populations at risk. Consequently, the ES outlined that 25(OH)D concentrations of 50 nmol/L do not assure maximum calcium metabolism, bone health, and muscle functioning in all individuals. The IOM, however, found no evidence that a serum 25(OH)D concentrations above 50 nmol/L have beneficial effects at a population level. According to the IOM, certain parameters mentioned as risk factors by endocrinologists (age, body mass index, skin pigmentation, latitude of residence, etc.) are part of the observed diversity among individuals in the general population. Therefore, there is no need to determine different recommendations for the screening and treatment of VDD for these specific subgroups. Moreover, the IOM report focused only on effects of vitamin D on skeletal health, whereas the higher optimal 25(OH)D levels suggested by the ES (above 75 nmol/L) were also based on its potentially beneficial extraskeletal actions.

In clinical settings, this lack of consensus makes decisions difficult, at least under certain clinical conditions. The various recommendations cannot be considered prescriptive for all

patients, and a one-size-fits-all strategy is still inconclusive. Recommendations based on data coming from observational studies conducted in specific populations and specific countries are likely not applicable for all individuals and cannot be generalized to other countries and settings. Physicians should consider different factors involved in the vitamin D status of their individual adolescent patients. Local circumstances (sunlight, season, food fortification policy, and medical costs) as well as individual determinants (factors or conditions favoring deficiency, clinical indications, and expected adherence to prescribed regimen) should always be taken into consideration when deciding about prevention and treatment of VDD. Providing education about risk factors for low vitamin D and encouraging regular outside physical activity and vigilant sun exposure is also important.

Conclusions: the prevention of VDD in adolescence remains a public health priority

Controversies on the role of vitamin D in adolescent health remain a challenging topic. Study groups that establish trustworthy guidelines should always describe their evaluation methodology and provide details on evidence. Although certain questions in relation to adolescents' vitamin D needs are left unanswered and the impact of vitamin D intake and status on many aspects of their health remains unclear, the prevention of VDD during this period of life remains a public health priority.

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